THE BULLETIN OF
Mathematical
BIOPHYSICS

HE UNIVERSITY OF CHICAGO PRESS · CHICAGO · ILLINOIS

OLUME 3
UMBER 3
EPT. 1941

THE BULLETIN OF Mathematical Biophysics

EDITED BY N. RASHEVSKY

The Bulletin is devoted to publications of research in Mathematical Biophysics, as described on the inside back cover.

THE BULLETIN is published by the University of Chicago at the University of Chicago Press, 5750 Ellis Avenue, Chicago, Illinois, quarterly, in March, June, September, December. ¶The subscription price is $2.50 per year, the price of single copies is 75 cents. Orders for service of less than a full year will be charged at the single-copy rate. ¶Patrons are requested to make all remittances payable to The University of Chicago Press in postal or express money orders or bank drafts.

THE FOLLOWING are authorized agents:

For the British Empire, except North America, India, and Australasia: The Cambridge University Press, Bentley House, 200 Euston Road, London, N.W. 1. Prices of yearly subscriptions and of single copies may be had on application.

For Japan: The Maruzen Company, Ltd., Tokyo.

For China: The Commercial Press, Ltd., 211 Honan Road, Shanghai.

CLAIMS FOR MISSING NUMBERS should be made within the month following the regular month of publication. The publishers expect to supply missing numbers free only when losses have been sustained in transit, and when the reserve stock will permit.

BUSINESS CORRESPONDENCE should be addressed to The University of Chicago Press, Chicago, Ill.

COMMUNICATIONS FOR THE EDITOR and manuscripts should be addressed to N. RASHEVSKY, Editorial Office of the Bulletin of Mathematical Biophysics, 5822 Drexel Avenue, Chicago, Ill.

PRINTED BY THE DENTAN PRINTING CO., COLORADO SPRINGS, COLORADO

BULLETIN OF
Mathematical Biophysics

CONTENTS

ELECTRICAL CHARGES AND POTENTIALS IN CELLS RESULTING FROM METABOLISM OF ELECTROLYTES - - - - - - - - - - - - 79
ROBERT R. WILLIAMSON

NOTE ON THE MATHEMATICAL BIOPHYSICS OF TEMPORAL SEQUENCES OF STIMULI - - - - 89
N. RASHEVSKY

A NOTE ON THE NATURE OF CORRELATIONS BETWEEN DIFFERENT CHARACTERISTICS OF ORGANISMS - - - - - - - - - - - - - - - 93
N. RASHEVSKY

MATHEMATICAL BIOPHYSICS OF THE GALVANIC SKIN RESPONSE - - - - - - - - - - - - 97
CLYDE H. COOMBS

A THEORY OF STEADY-STATE ACTIVITY IN NERVE-FIBER NETWORKS: II. THE SIMPLE CIRCUIT - 105
ALSTON S. HOUSEHOLDER

VOLUME THREE SEPTEMBER 1941 NUMBER THREE

BULLETIN OF
MATHEMATICAL BIOPHYSICS
VOLUME 3, 1941

ELECTRICAL CHARGES AND POTENTIALS IN CELLS RESULTING FROM METABOLISM OF ELECTROLYTES

ROBERT R. WILLIAMSON
THE UNIVERSITY OF CHICAGO

An approximate solution for the relation of the charges and potentials in a spherical cell to the production of electrolytes in the cell and their diffusion resistances is derived. The potential obtained by introducing reasonable values of the constants is of the proper order of magnitude. The equations are applied to a respiratory chain and the relation between oxygen consumption, glycolytic coefficient, and potentials is determined. Available experimental data is compared with the theory.

In the following derivations we will use these notations.

D_+ = diffusion coefficient of the positive ion in $cm^2\ sec^{-1}$,

D_- = diffusion coefficient of the negative ion in $cm^2\ sec^{-1}$,

h_+ = membrane permeability of the positive ion in cm sec^{-1},

h_- = membrane permeability of the negative ion in cm sec^{-1},

Q = rate of production of ions in mol $cm^{-3}\ sec^{-1}$,

C = internal concentration in mol cm^{-3},

C_0 = external concentration in mol cm^{-3},

r_0 = radius inside membrane in cm,

δ = membrane thickness in cm,

T = absolute temperature in deg A.,

f = electrical force on an ion due to field of other ions.

k = Boltzmann constant = $1.4 \cdot 10^{-16}$ erg deg^{-1},

ε = charge on an electron = $4.8 \cdot 10^{-10}$ abs. E. S. units,

ρ = charge density,

K = dielectric constant,

$A = \dfrac{4\pi r_0^2 N \varepsilon^2}{Kkt} = 4.7 \cdot 10^{12}$, with values chosen previously. (Williamson 1939),

N = Avogadro's number = $6.06 \cdot 10^{23}$ molecules mol^{-1},

J = transport in mol cm^{-2} sec^{-1},

B = mobility of an ion in cm^2 erg^{-1} t^{-1},

Λ_+ = diffusion resistance of the positive ion in sec,

$$= \frac{r_0^2}{6D_+} + \frac{r_0}{3h_+}$$

Λ_- = diffusion resistance of the negative ion in sec,

$$\lambda = \frac{r_0^2}{12} \cdot \frac{D_+ + D_-}{D_+ D_-} + \frac{r_0}{6} \frac{h_+ + h_-}{h_+ h_-} = \frac{\Lambda_+ + \Lambda_-}{2} \text{ in sec},$$

$P.D.\Big|_{r_1}^{r_2}$ potential difference between r_1 and r_2 in abs. E. S. volts.

Denote by a bar average, by a + or − subscript the ions to which the quantity refers, and by a subscript 1, values at the membrane, by subscript 0, external values, except r_0, radius of cell.

Assume a cell of two phases, spherically symmetric, one extending from 0 to r_0 and the other constituting a shell of thickness δ corresponding to a membrane. Assume a non-electrolyte to be metabolized producing an electrolyte. If the diffusion resistances are different for the ions of opposite charge, there will be a difference in concentration which will result in a net charge. If we assume the distribution of the ions to be linear, the charge density, given at a point by

$$\rho = N \varepsilon \Delta, \text{ where } \Delta = C_+ - C_-, \tag{1}$$

will also be a linear function of r.

Let

$$\rho = ar + b, \text{ where } 0 \leq r < r_0 \text{ (inner phase)},$$

and

$$\rho = a_1 r + b_1 \text{ where } r_0 \leq r \leq r_0 + \delta \text{ (outer phase)}. \tag{2}$$

The force, resulting from the charge, on a unit charge at a point r is given by: (Joos, 1934)

$$F = \frac{E}{Kr^2}, \text{ where } E = 4\pi \int_0^r \rho(r) \cdot r^2 \, dr. \tag{3}$$

The potential difference between any two points r_1, r_2 is

$$P.D.\Big|_{r_1}^{r_2} = -\int_{r_2}^{r_1} F\,dr\,. \tag{4}$$

In the inner phase

$$\begin{aligned} P.D.\Big|_{r_1}^{r_2} &= -\frac{4\pi}{K}\int_{r_2}^{r_1}\frac{dr}{r^2}\int_0^r r^2\,\rho(r)\,dr\,, \\ &= -\frac{4\pi}{K}\left[\frac{a}{12}(r_1^3 - r_2^3) + \frac{b}{6}(r_1^2 - r_2^2)\right], \end{aligned} \tag{5}$$

and if $r_1 = 0$, and $r_2 = r_0$,

$$P.D.\Big|_0^{r_0} = \frac{2\pi r_0^2}{3K} N\varepsilon\bar{\Delta}\,, \tag{6}$$

if we let $\bar{\Delta} = \Delta$ at $r_0/2$.

In the membrane, equation (5) applies, but $\rho(r) = ar + b$ or $a_1 r + b_1$ according to equations (2). Therefore,

$$\begin{aligned} \int_0^r r^2\cdot\rho(r)\,dr &= \frac{a-a_1}{4}r_0^4 + \frac{b-b_1}{3}r_0^3 + \frac{a_1 r^4}{4} + \frac{b_1 r^3}{3}\,. \\ P.D._m = P.D.\Big|_{r_0}^{r_0+\delta} &= \frac{\pi\delta}{3K}\left[3ar_0^2 + 4br_0\right], \end{aligned} \tag{7}$$

when second and higher powers of δ/r_0 are neglected.

Δ is a function of r. By the standard reasoning used in the approximation method (Rashevsky, 1940), we consider that C has approximated the values $\bar{C}$ when $r = r_0/2$. Similarly we define C_1 as the value of C for $r = r_0$. Then let

$$\begin{aligned} \bar{\Delta} &= \bar{C}_+ - \bar{C}_-\,, \\ \Delta_1 &= C_{1+} - C_{1-}\,, \end{aligned} \tag{8}$$

and let $D_{e+} = D_{e-} = \infty$.

Then from equations (1), (2), and (8)

$$\begin{aligned} a &= -\frac{2N\varepsilon}{r_0}(\bar{\Delta} - \Delta_1), \text{ and} \\ b &= N\varepsilon(2\bar{\Delta} - \Delta_1). \end{aligned} \tag{9}$$

Introducing these values into equation (7) we have

$$P.D.\Big|_m = \frac{2\pi r_0\,\delta N\varepsilon}{3K}(\bar{\Delta} + \Delta_1)\,. \tag{10}$$

Now we must evaluate $\bar{\Delta}$, Δ_1, from the diffusion equations. In the stationary state the material balance equations are

$$J_+ = J_-; \quad J_1 = J_0; \quad J = \frac{Qr_0}{3}. \tag{11}$$

The equations for the transport may all be expressed in the form (Reiner, 1937, Williamson, 1939)

$$J = -D \operatorname{grad} C + Bfc,$$

where (Gyemant, 1925, p. 55) $B = D/kT$.

If we take an average gradient and force on the ions (N. Rashevsky, 1940), and introduce the subscript notation we obtain from the above equation the following four steady state equations for transport of respectively, positive ion in the inner phase, positive ion in the outer phase, negative ion in the inner phase, and negative ion in the outer phase, after slight rearrangements.

$$\frac{Qr_0^2}{6D_+} = \bar{C}_+ - C_{1+} + \frac{2\pi r_0^2 N \varepsilon^2}{KkT} (\bar{C}_+ - \bar{C}_-)\bar{C}_+, \tag{12}$$

$$\frac{Qr_0}{3h_+} = C_{1+} - C_{0+} + \frac{2\pi r_0 \delta N \varepsilon^2}{KkT} (\bar{C}_+ - \bar{C}_-)(C_{1+} + C_{0+}); \tag{13}$$

and

$$\frac{Qr_0^2}{6D_-} = \bar{C}_- - C_{1-} - \frac{2\pi r_0^2 N \varepsilon^2}{KkT} (\bar{C}_+ - \bar{C}_-)\bar{C}_-, \tag{14}$$

$$\frac{Qr_0}{3h_-} = C_{1-} - C_{0-} - \frac{2\pi r_0 \delta N \varepsilon^2}{KkT} (\bar{C}_+ - \bar{C}_-)(C_{1-} + C_{0-}). \tag{15}$$

Adding equations (12) and (13), and (14) and (15), we have

$$\Lambda_+ Q = \bar{C}_+ - C_{0+} + \frac{A}{2} (\bar{C}_+ - \bar{C}_-)\left[\bar{C}_+ + \frac{\delta}{r_0}(C_{1+} + C_{0+})\right],$$

$$\Lambda_- Q = \bar{C}_- - C_{0-} - \frac{A}{2} (\bar{C}_+ - \bar{C}_-)\left[\bar{C}_- + \frac{\delta}{r_0}(C_{1-} + C_{0-})\right].$$

Or since $A \sim 10^{12}$, $\delta/r_0 \sim 10^{-3}$ or less

$$\Lambda_+ Q = \frac{A}{2} (\bar{C}_+ - \bar{C}_-)\bar{C}_+, \quad \Lambda_- Q = -\frac{A}{2} (\bar{C}_+ - \bar{C}_-)\bar{C}_-$$

$$(\Lambda_+ - \Lambda_-) Q = \frac{A}{2} (\bar{C}_+^2 - \bar{C}_-^2).$$

If we introduce the notation

$\bar{C}_+ = \bar{C} + \bar{\Delta}_+$, $\bar{C}_- = \bar{C} + \bar{\Delta}_-$, expand, and drop powers of $\bar{\Delta}_+$ or $\bar{\Delta}_-$ higher than the first, we have

$$\frac{\Lambda_+ - \Lambda_-}{A\,C} Q = \bar{\Delta}_+ - \bar{\Delta}_- = \bar{\Delta}. \tag{16}$$

Collecting C_{1+}, C_{1-} in equations (13) and (15) we have

$$\left(\frac{A\,\delta}{2r_0}\bar{\Delta} + 1\right) C_{1+} = \frac{Qr_0}{3h_+} + C_0\left[1 - \frac{A\,\delta}{2r_0}\bar{\Delta}\right],$$

$$\left(1 - \frac{A\,\delta\,\bar{\Delta}}{2r_0}\right) C_{1-} = \frac{Qr_0}{3h_-} + C_0\left[1 + \frac{A\,\delta\,\bar{\Delta}}{2r_0}\right].$$

If we divide by the coefficient of C_1, apply the binomial expansion and consider only the first two terms of the expansion, we have

$$C_{1+} = \frac{Qr_0}{3h_+}\left[1 - \frac{A\,\delta\,\bar{\Delta}}{2r_0}\right] + C_0\left[1 - \frac{A\,\delta\,\bar{\Delta}}{2r_0}\right]^2,$$

$$C_{1-} = \frac{Qr_0}{3h_-}\left[1 + \frac{A\,\delta\,\bar{\Delta}}{2r_0}\right] + C_0\left[1 + \frac{A\,\delta\,\bar{\Delta}}{2r_0}\right]^2;$$

or

$$\Delta_1 = -\frac{Qr_0}{3}\left[\frac{h_+ - h_-}{h_+h_-} + \frac{A\,\delta\,\Delta}{2r_0}\cdot\frac{h_+ + h_-}{h_+h_-}\right] - \frac{2C_0\,A\,\delta\,\Delta}{r_0}.$$

Choosing the following plausible values, (Rashevsky, 1940; R. Höber, 1936)

$h_+ = 10^{-5}$ cm^2 sec^{-1}; $h_- = 10^{-3}$ cm^2 sec^{-1}; $\delta = 5 \cdot 10^{-7}$ cm;

$\Lambda_+ = 2$ sec; $\Lambda_- = 200$ sec; $\lambda = 100$ sec; $K = 80$;

$C_0 = 10^{-6}$ mol cm^{-3}; $Q = 10^{-7}$ mol cm^{-3} sec^{-1};

we see that

$$\left|\frac{h_+ - h_-}{h_+h_-}\right| >> \frac{A\,\delta\,\bar{\Delta}}{2r_0}\frac{h_+ + h_-}{h_+h_-} >> \frac{2\,A\,\delta\,\bar{\Delta}}{Qr_0^2}C_0,$$

and we may write this equation with little error as

$$\Delta_1 = -\frac{Qr_0}{3}\frac{h_+ - h_-}{h_+h_-}.$$

Finally, if we let $\bar{C} = \lambda\,Q + C_0$

$$P.D.\Big|_0^{r_0} = \frac{kT}{6\varepsilon}\frac{\Lambda_+ - \Lambda_-}{\lambda Q + C_0}Q = \frac{kT}{6\varepsilon}\left|\frac{\Lambda_+ - \Lambda_-}{\lambda + C_0/Q}\right.,$$

and

$$P.D.\Big|_m = \frac{\delta}{r_0} P.D.\Big|_0^{r_0} - \frac{2\pi r_0^2 N \varepsilon^2 \delta}{9K} \frac{h_+ - h_-}{h_+ h_-} Q.$$

or

$$P.D.\Big|_0^{r_0+\delta} = \frac{kT}{6\varepsilon} \frac{\Lambda_+ - \Lambda_-}{\lambda + C_0/Q} \left(1 + \frac{\delta}{r_0}\right) - \frac{2\pi r_0^2 \delta N \varepsilon}{9K} \frac{h_+ - h_-}{h_+ h_-} Q.$$

With the values chosen this gives a potential difference of -41.2 millivolts, of which -37.5 are across the membrane.

If we consider a respiratory system such as discussed by A. T. Cameron (1930), and H. D. Landahl (1939),

$$\underset{(1)}{\text{glucose}} + \underset{(6)}{\text{phosphate}} \overset{a}{\rightleftarrows} \underset{(7)}{\text{hexosediphosphate}} \overset{g}{\rightleftarrows} \underset{(2)}{\text{lactic acid}} + \underset{(6)}{\text{phosphate}}$$

$$+$$

$$\underset{(4)}{\text{carbon dioxide}} + \underset{(5)}{\text{water}} \overset{f}{\leftarrow} \underset{(3)}{\text{oxygen}},$$

we have

$$q_1 = -a\bar{C}_1\bar{C}_6,$$

$$q_2 = -nf\bar{C}_2\bar{C}_3 + g\bar{C}_7,$$

$$q_3 = -f\bar{C}_2\bar{C}_3,$$

$$q_6 = -Q_7 = -a\bar{C}_1\bar{C}_6 + g\bar{C}_7 = 0,$$

$$C_p = \bar{C}_6.$$

We may obtain

$$q_2 = nq_3 - q_1,$$

$$Q_2 = nQ_3 \frac{M_3}{M_2} - \frac{M_1}{M_2} Q_1.$$

If one mol of (1) is oxidized, 3β are glycolyzed and $3\beta + 1$ are used. But for oxidation of 1 mol of (1), $6O_2$ are used, and

$$Q_3 = 6Q_1 \text{ for oxidation,}$$

or

$$Q_1 = (3\beta + 1)\frac{Q_3}{6},$$

and

$$Q_2 = \frac{Q_3}{3} - \frac{(3\beta + 1)Q_3}{3},$$

since

$$n = \frac{M_2}{3M_3}:$$

Then

$$Q_2 = -\beta Q_3 \text{ or } \beta = -\frac{Q_2}{Q_3}.$$

If we identify Q with lactic acid, and assume for a preliminary investigation that it is highly ionized and that there is no adsorption of either ion, or that the diffusion coefficient is that of the adsorbing particle after adsorption, we have then

$$P.D.\Big|_0^r = \frac{kT}{6\varepsilon}\frac{\Lambda_+ - \Lambda_-}{\bar{C}_2} Q_2 = -\frac{kT\beta}{6\varepsilon}\frac{\Lambda_+ - \Lambda_-}{\bar{C}_2} Q_3,$$

$$= +\frac{fkT\beta}{2\varepsilon}(\Lambda_+ - \Lambda_-)\, m\bar{C}_3,$$

where $m = \dfrac{M_2}{3M_3}$

$$P.D.\Big|_0^{r_0+\delta} = P.D.\Big|_0^{r_0}(1 + \frac{\delta}{r_0}) + \frac{2\pi r_0^2 \delta N \varepsilon \beta}{9K}\frac{h_+ - h_-}{h_+ h_-} Q_3,$$

$$= P.D.\Big|_0^{r}(1 + \frac{\delta}{r_0}) - \frac{2\pi r_0^2 \delta N \varepsilon \beta f m}{3K}\frac{h_+ - h_-}{h_+ h_-}\bar{C}_2\bar{C}_3.$$

E. J. Lund (1931) gives data relating electrical polarity potentials to oxygen consumption at different temperatures. Since his oxygen consumption is measured as an average over a three hour period, we cannot say that the peaks and depressions in the polarity potential curve are not due to a variation in O_2 consumption, since such variations were not determined. In fact, we find indicated just such a variation with O_2 consumption if we consider the probable variation of O_2 consumption with temperature. For T. C. Barnes (1937) cites the experiments of T. C. Barnes and T. L. Jahn (1933) in which the previous temperature variations of water had an effect on Euglenia activity, previously cooled water having a stimulating effect. T. C. Barnes ascribes this to formation of the trihydrol polymer. F. W. Gray and J. H. Cruickshank (1935) found a lag in diamagnetic susceptibility of water recently melted, of 20 minutes to the maximum and subsequent subsidence to a constant value, supposedly a hysterisis lag in polymer equilibrium. In E. J. Lund (1931), plate 1, we see a peak in potential reached about 20 to 30 minutes after the increase in temperature. Correspondingly there is sometimes a significant depression below the base line when the temperature is lowered, rather than a monotonic approach to equilibrium of the same time interval. This is also observed in Douglas fir (Lund, 1932a, 1932b). We see then that Lund's

data could be interpreted as a correlation of potential difference and metabolic activity in which the lag in activity with temperature variation is due to a hysteresis lag in attaining equilibrium of the water polymers. This would support our theory, but more information as to the variation of O_2 consumption, *P.D.*, and temperature is needed. This effect might also be explained as the result of an accumulation of intermediate products at low temperatures which would create an excess activity for a brief period after return to a higher temperature. However, attempts to store free oxygen and other substances in cells have been relatively unsuccessful.

We have shown that continuously maintained potentials resulting from diffusion are of the correct order of magnitude, and vary in the proper way with cell metabolism. Such potentials may play a role in nerve excitation, protoplasmic streaming, flow of sap in plants, etc., but the forces are too small to be of importance in cell division when compared to diffusion forces. These potentials will vanish with death of the cell as contrasted to potentials derived from colloid adsorption or Donnan membrane permeability (N. Rashevsky, 1935, 1938, 1940).

The author is indebted to Dr. N. Rashevsky for his frequent and invaluable aid, and to Dr. A. S. Householder for checking and correcting the manuscript.

This work was aided in part by a grant from the Dr. Wallace C. and Clara A. Abbott Memorial Fund of the University of Chicago.

LITERATURE

Barnes, T. C. 1937. *Textbook of General Physiology.* Philadelphia: P. Blakiston's Sons.

Barnes, T. C. and T. L. Jahn. 1933. "The Effect of Ice and Steam Water on Euglena." *Proc. Nat. Acad. Sci.*, **19**, 638-640.

Cameron, A. T. 1930. *A Textbook of Biochemistry.* London: J. and A. Churchill.

Gray, F. W. and J. H. Cruickshank. 1935. "Diamagnetism of Light and Heavy Water." *Nature*, **135**, 268-269.

Gyemant, Andreas. 1925. *Grundzüge der Kolloidphysik.* Braunschweig: Viewig und Sohn.

Höber, R. 1936. "Membrane Permeability to Solutes in Its Relation to Cellular Physiology." *Physiol. Rev.*, **16**, 52-102.

Joos, G. 1934. *Theoretical Physics.* London: Blackie and Son Ltd.

Landahl, H. D. 1939. "Mathematical Biophysics of Cell Respiration II." *Bull. Math. Biophysics*, **1**, 1-17.

Lund, E. J. and J. B. Moorman. 1931. "Electrical Polarity and Velocity of Cell Oxidation as Functions of Temperature." *Jour. Exp. Zool.*, **60**, 249-267.

Lund, E. J. 1932a. "Control of the Flux Equilibrium of Electrochemical Processes and Electric Polarity in the Douglas Fir by Temperature." *Plant Physiology*, **7**, 297-307.

Lund, E. J. 1932b. "Comparison of the Effects of Temperature on the Radial and Longitudinal Electric Polarities in Wood and Cortex of the Douglas Fir." *Plant Physiology*, **7**, 505-516.

Rashevsky, N. 1935. "On Electric Charges of Disperse Systems Which Are the Seats of Physico-Chemical Reactions." *Physics*, **6**, 33-34.

Rashevsky, N. 1938. *Mathematical Biophysics: Physicomathematical Foundations of Biology*. Chicago: University of Chicago Press.

Rashevsky, N. 1940. *Advances and Applications of Mathematical Biology*. Chicago: University of Chicago Press.

Reiner, J. 1937. "Diffusion and Biological Membrane Permeability I." *Growth*, **1**, 313-327.

Williamson, Robert R. 1939. "A Comparison of Electrical and Diffusion Forces in the Metabolism of Electrolytes." *Bull. Math. Biophysics*, **1**, 151-157.

BULLETIN OF
MATHEMATICAL BIOPHYSICS
VOLUME 3, 1941

NOTE ON THE MATHEMATICAL BIOPHYSICS OF TEMPORAL SEQUENCES OF STIMULI

N. RASHEVSKY
THE UNIVERSITY OF CHICAGO

Some general considerations are given regarding the effects of temporal sequences of stimuli in a neuronic network, which consists of a set of parallel chains of excitatory fibers with cross-connections made of inhibitory fibers. It is shown that, in general, the excitation produced by any individual stimulus of the series is a function of the order and duration of the previous stimuli, and that the effect of each stimulus thus depends on the whole temporal pattern considered.

In the mathematical biophysics of the central nervous system hitherto only the effects of a number of stimuli applied simultaneously, have been considered. The only exception is an important paper by H. D. Landahl (1940), in which a special case of two temporally separated stimuli are considered. It has been shown elsewhere (Rashevsky, 1938, hereinafter referred to as MB), that in general the problem of temporal sequence of stimuli reduces to a problem of a set of rather complex integro-differential equations (MB, p. 238). The very complexity of those equations and their rather unusual mathematical form, makes their usefulness for practical purposes at present rather

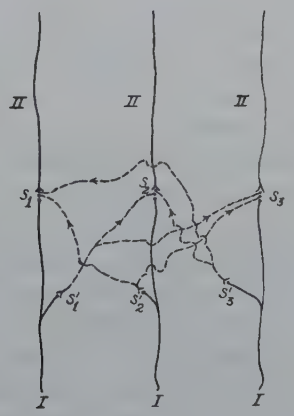

FIGURE 1

To each fiber of type I corresponds a different stimulus S_i. The synapses between fibers of type I and fibers of type II are marked by s_i. In this figure we have s_1, s_2 and s_3, corresponding to $i = 1, 2, 3$. A fiber of type II, corresponding to the synapse s_i is referred in the text as fiber II_i.

doubtful. The purpose of the present paper is to outline a somewhat more restricted problem, the mathematical treatment of which does not involve any complexities at all, and which at the same time presents a definite biophysical interest.

Consider the usual scheme of a set of parallel excitatory chains, with inhibitory cross-connections (Figure 1). The properties of this simple structure have been studied from many angles and applied to varied cases (MB, chapter xxii ff.). Let us consider at once a more general case, by assuming that while the constants of all the excitatory fibers are the same, those of the inhibitory fibers are all different. If we consider, under these conditions, two stimuli, S_k and S_l, applied to two different fibers of type I, then the inhibitory effect J_{kl} of S_k upon the synapse s_l corresponding to S_l is not the same as the inhibitory effect J_{lk} of S_l upon the synapse s_k corresponding to S_k, even when the intensities of S_k and S_l are equal. Furthermore let us consider the case, that all fibers are of the general type, every fiber producing both ε and j. The excitatory fiber produces an excess of ε, the inhibitory — an excess of j. Let the former be characterized by

$$A > B; \quad a > b; \quad \frac{A}{a} > \frac{B}{b}; \tag{1}$$

while the latter are characterized by

$$A < B; \quad a < b; \quad \frac{A}{a} < \frac{B}{b}. \tag{2}$$

Let now a stimulus S_k of constant intensity, sufficient to produce an excitation in the corresponding fiber *II* (Figure 1), be suddenly applied and sustained for some time. This results in an excitation of one corresponding center at the efferent end of fiber *II*, and in an inhibition of all synapses corresponding to other stimuli S_i. Let now at some moment t the stimulus S_k be suddenly interrupted. With inhibitory fibers characterized by inequalities (2), this will result in temporary excesses of ε over j, produced by all inhibitory fibers, stimulated by S_k, at all synapses, corresponding to other stimuli (MB, p. 228). The intensity of this "rebound phenomenon" will depend at each synapse upon the physical constants of the inhibitory fiber producing it, and upon the intensity of S_k. The time of onset of this rebound phenomenon, at which ε becomes greater than j, will be independent of the intensity of S_k. It will, however, depend on the duration of S_k.

Thus the mere *cessation of a stimulus* results in certain excitatory phenomena, and by an appropriate neural mechanism ***may be perceived itself as a stimulus.***

For the present let us assume that the rebound phenomenon at all the synapses is not strong enough to excite any of the fibers *II*. Under those conditions the cessation of S_k will not excite any of the fibers *II*. But if after its cessation, S_k is followed shortly by another stimulus S_l, (applied, of course, to a different fiber of type *I*) then the excitation of the fiber *II*, corresponding to S_l will be greater, than if S_l were not preceded by S_k. Inversely, the effect of S_k is altered by making it be preceded by S_l. Due to $J_{kl} \gtrless J_{lk}$, the two effects are, however, not identical quantitatively. The maximum value of excitation produced in the two corresponding fibers *II* by the sequence $S_k\ S_l$ is different from the maximum value produced by the sequence $S_l\ S_k$, and in general they are both different from the maximum value produced by a simultaneous application of S_k and S_l. Moreover, the effect of the combination $S_k\ S_l$ will depend both on the duration of S_k and S_l and upon the time interval between them. The rebound phenomenon at each synapse starts at zero, reaches a maximum and then drops again to zero. Therefore, a maximum increase in the intensity of excitation of II_l due to a preceding S_k will be reached when a definite time t^* elapses between the cessation of S_k and the initiation of S_l. This time t^* is, however, not identical with the time t_m at which the rebound value of $\varepsilon - j$ reaches a maximum (MB, p. 228), because ε_k and j_k do develop gradually after the application of S_k.

Consider now a sequence of stimuli S_i, S_k, $S_l \cdots S_r$, each having a corresponding duration t_i, t_k, $t_l \cdots t_r$. Denote the time interval between S_i and S_k by t_{ik}. Denoting the rebound intensity at s_l due to S_k by R_{kl}, the quantity R_{kl} will be a function of S_k, t_k and t_{kl}. The intensity of excitation of II_r will be determined by all the previous S's, their durations and the intervals between them. For that intensity is determined by the amount

$$\varepsilon_r - j_r + \sum_p R_{pr}, \tag{3}$$

the summation being taken over all previous stimuli.

A still more complex situation obtains when we consider the scheme of Figure 2, in which the inhibitory fibers start at the synapses s_i (MB, p. 235). In that case even every R_{pr} depends upon all previous S's and all previous R_{sp}'s. We have here an analogy to the phenomenon, emphasized by many psychologists, namely that the effect of a stimulus in a series of others is determined by the "time gestalt" of those other stimuli, or, if we may say so, by its "context".

In the case represented on Figure 1, the effect of a stimulus is always enhanced by preceding stimuli, the amount of enhancement depending on the past sequences of stimuli. In the case, however, of

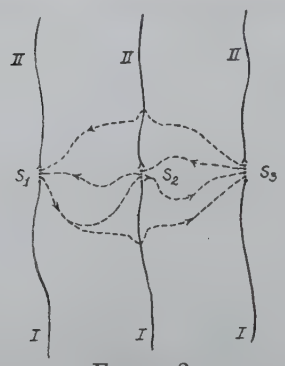

FIGURE 2

Figure 2, a preceding stimulus may *reduce* the response to a given stimulus. For the cessation of a preceding stimulus results in a rebound excitation at *all* synapses, and this rebound excitation excites the inhibitory fibers, leading to the synapse under consideration. That synapse has now a rebound excitation from the synapse corresponding to the preceding stimulus and an inhibition due to the rebound excitation at all other synapses. The total "time gestalt" of the preceding stimuli will determine which of the two effects prevails, and whether the effect of the given stimulus is enhanced or reduced by previous stimuli.

LITERATURE

Landahl, H. D. 1940. "Discrimination Between Temporally Separated Stimuli." *Bull. Math. Biophysics*, **2**, 37-47.

Rashevsky, N. 1938. *Mathematical Biophysics. Physicomathematical Foundations of Biology.* Chicago. The University of Chicago Press.

Rashevsky, N. 1940. *Advances and Applications of Mathematical Biology.* Chicago. The University of Chicago Press.

BULLETIN OF
MATHEMATICAL BIOPHYSICS
VOLUME 3, 1941

A NOTE ON THE NATURE OF CORRELATIONS BETWEEN DIFFERENT CHARACTERISTICS OF ORGANISMS

N. RASHEVSKY
THE UNIVERSITY OF CHICAGO

Different anatomical and physiological characteristics of organisms affect their interreaction with the inorganic world as well as their mutual interreactions. In this way they all may affect indirectly the total rate of reproduction of a species. It is shown that the requirement of a maximum rate of reproduction defines the distribution functions of the different characteristics and through those distribution functions determines statistical correlations between the characteristics.

The relation between different characteristics of an organism is in many cases due to the biophysical constants of the organism itself. If two different characteristics x and y are determined by the same physico-chemical factors, there will be a definite quantitative relation between those two characteristics. If, however, the two characteristics are determined in general by two different groups of factors, with only a few factors being common to the two groups, we shall find instead of a definite mathematical relation between x and y, only a certain correlation, which will be the closer to unity, the more common factors the two groups possess. The future development of the mathematical biophysics of the organisms as a whole should thus eventually lead us to the theoretical prediction of the correlation coefficients between different pairs of characteristics of an organism. Such a theory would be of particular value because it will render useful a wealth of empirical data accumulated in this field by biometrists.

It must be pointed out, however, that there is another possible cause for the appearance of correlation between different characteristics of an organism. This cause lies in the effects which these given characteristics may have upon the interaction of different organisms and thus indirectly upon the preservation of the species. Certain pairs of values of the two characteristics may be more favorable to the preservation of the species. Organisms characterized by such pairs of values will have a better chance for survival and such pairs of values will therefore occur more frequently than one would expect on the basis of a random distribution. The purpose of this note is to discuss briefly

the general type of mathematical problems, to which considerations of the above mentioned kind may lead.

Let us first consider the case, that the two characteristics x and y vary discontinuously, and may have only discreet values, x_1, x_2, x_3, $\cdots$ x_n; y_1, y_2, y_3 $\cdots$ y_n. Let the number of organisms, characterized by the values, x_i, y_k be equal to N_{ik}. We shall refer to an organism, characterized by x_i, y_k as organism (ik). The values x_i and y_k determine amongst other things, the interaction of the particular organism with its inorganic surroundings; and through that interaction they determine the rate of net increase $a_{ik}N_{ik}$ with respect to time of the organism of that kind. But that rate of increase also depends on the interaction of the organism (ik) with other organisms (ik) as well as organisms (mn), where m and n are different from i and k. We may set that part of the rate of increase as being of the form

$$N_{ik} \sum_{n} \sum_{m} b_{ik}^{mn} N_{mn}. \tag{1}$$

We thus have for the total rate of increase of all organisms

$$N = \sum_{i} \sum_{k} N_{ik} \tag{2}$$

the expression

$$\frac{dN}{dt} = \sum_{i} \sum_{k} a_{ik} N_{ik} + \sum_{i} \sum_{k} N_{ik} \sum_{m} \sum_{n} b_{ik}^{mn} N_{mn}. \tag{3}$$

The natural selection acts so as to maximize expression (3), and the conditions of the maximum of (3) give us the values of N_{ik}'s. These we determine by

$$\frac{\partial}{\partial N_{ik}} \left(\sum_{i} \sum_{k} a_{ik} N_{ik} + \sum_{i} \sum_{k} N_{ik} \sum_{m} \sum_{n} b_{ik}^{mn} N_{mn} \right) = 0 \tag{4}$$

and this gives a system of equations

$$a_{ik} + \sum_{m} \sum_{n} b_{ik}^{mn} N_{mn} = 0. \tag{5}$$

By a procedure familiar in the theory of integral equations, we may pass to the case of continuously varying x's and y's. In this case the a_{ik}'s and the N_{mn}'s become functions $a(x, y)$ and $N(\xi, \zeta)$ of x and y, and ξ and ζ. The coefficients b_{ik}^{mn} become functions $b(x, y, \xi, \zeta)$ of four variables. The system of linear equations (5) reduces to the integral equation:

$$a(x, y) + \iint b(x, y, \xi, \zeta) N(\xi, \zeta) \, d\xi d\zeta = 0. \tag{6}$$

where $a(x, y)$ and $b(x, y, \xi, \zeta)$ are known. The solution of (6)

gives us the distribution function $N(x, y)$ for both characteristics. This function $N(x , y)$ determines the average values $\bar{x}$ and $\bar{y}$ of the characteristics. The correlation coefficient between x and y is then given by

$$r = \frac{\overline{(x - \bar{x})(y - \bar{y})}}{\sqrt{\overline{(x - \bar{x})^2 (y - \bar{y})^2}}}, \tag{7}$$

and is completely determined by $N(x , y)$.

The solution of the integral equation (6) represents the *mathematical* problem involved in the development of the suggested theory. The *biophysical* problem lies in the determination of $a(x , y)$ and of $b(x , y , \xi , \zeta)$, and represents a different problem for every different meaning of x and y . For instance, x may stand for the weight of the animal, and y for its speed of locomotion. In determining $b(x , y , \xi , \zeta)$ we will have to consider that a large x is beneficial for the preservation of the species by offering a protection against smaller enemies. A large y is also beneficial, by enabling avoidance of enemies on one hand and catching prey on the other. But the effect of ξ and ζ is opposite. In general in this case $b(x , y , \xi , \zeta)$ will increase with x and y and decrease with ξ and ζ .

The salient feature of the situation is that the characteristics of an organism depend on the structure of the whole organic world. A particular distribution function $N(x , y)$ is determined by its contribution to the maximalization of the rate of reproduction of the organic world as a whole, and not of a particular species. We thus may find that certain characteristics of an organism exist, which are of no apparent use to *that* organism (C.f. appendix and caecum).

We may set approximately $b(x , y , \xi , \zeta)$ and $a(x , y)$ as linear functions of x , y , ξ and ζ , with indeterminate coefficients, and then determine these coefficients from the observed correlations.

BULLETIN OF
MATHEMATICAL BIOPHYSICS
VOLUME 3, 1941

MATHEMATICAL BIOPHYSICS OF THE GALVANIC SKIN RESPONSE

CLYDE H. COOMBS
THE UNIVERSITY OF CHICAGO
(At present: Personnel Research Section, Adjutant General's Office, War Department, Washington, D. C.)

Beginning with Rashevsky's equation for the development of the excitatory state in a nerve fiber, an equation for the change in skin resistance upon the presentation of an instantaneous stimulus is derived. The mechanism assumed is in conformity with the existing evidence of neuro-physiology. Certain deductions from the equations are made and experimental problems suggested for testing the theory.

One of the most perplexing problems faced by the physiological psychologist is the problem of how to measure the galvanic skin response. Upon presentation of a stimulus, a curve indicating the change in the apparent skin resistance is secured. The basis of the problem lies primarily in the fact that there is no clear idea of the nature of the biophysical mechanism mediating the response and hence no clear idea of the significance of the various parameters of the curve.

There is, however, sufficient evidence (Richter, 1929a; O'Leary, 1932; Darrow, 1934; Dale, 1936; Rashevsky, 1938) from a variety of sources which may be integrated to provide a reasonable hypothesis for the biophysical mechanism. Deriving an equation for the change in skin resistance from a quantitative expression of the hypothesis will, when fitted to the data, yield parameters that have physiological and psychological significance.

That the galvanic skin response undoubtedly has a very complex mechanism with a variety of factors interacting is agreed upon by all workers in the field. But it is not until quantitative expression is given to hypotheses as to the nature of the interaction that the validity of the hypotheses may be checked against experimental data.

In a first attempt to develop a quantitative theory, it would be futile to try to include all of the great variety of factors that conceivably might enter into the determination of the finally observed response. In a first approximation we shall select only those factors which we consider to be of fundamental importance and impose the simplest experimental conditions upon the equations. If the experimental data are in general agreement with the predictions of the

equations we may then feel that we are on the right track. The next step is to complicate the experimental conditions, making no change in the postulates in regard to the biophysical mechanism, until a point is reached at which the experimental data fails to conform to the theory. This would then indicate that one or more of the factors previously neglected in the development of the equations has, with the more complex experimental conditions, become important; and a second approximation or extension of the theory is in order.

On the basis of the sources previously referred to, the biophysical mechanism hypothesized as underlying the galvanic skin response is, in its simplest form, as follows. Upon presentation of a stimulus above some threshold an excitation of the autonomic nerves mediating the galvanic skin response occurs. The intensity of the stimulus applied to the autonomic nerves we shall designate by the letter E. An excitatory state (ε) is developed in the autonomic nerves at a rate proportional to E, and is dissipated at a rate proportional to itself. A chemical mediator (p_p) is produced at the peripheral end of the autonomic fibers as a result of the excitatory state, and diffuses to the sweat gland tissue, in the neighborhood of which it is designated as p_d. We shall further assume that p_d bears an inverse relation to the apparent skin resistance.

This hypothesis may be developed quantitatively in the following manner.

The development of ε is given by N. Rashevsky (1938, chap. xxii)

$$\frac{d\varepsilon}{dt} = A' E - a\,\varepsilon. \tag{1}$$

Introducing a change of variable

$$at = \tau$$

$$A = \frac{A'}{a}$$

$$a\,dt = d\,\tau$$

and substituting in (1)

$$\frac{d\varepsilon}{d\tau} = A\,E - \varepsilon. \tag{2}$$

The quantity ε varies according to

$$\varepsilon = A\,E(1 - e^{-\tau}). \tag{3}$$

In the absence of any stimulus E, equation (2) takes the form

$$\frac{d\varepsilon}{d\tau} = -\varepsilon \tag{4}$$

and the quantity ε varies according to

$$\varepsilon = \varepsilon_1 e^{-\tau} \tag{5}$$

where ε_1 is the value which ε has at the moment the stimulus ceases.

The simplest experimental condition which we may impose is the case of an instantaneous stimulus, where the duration of the stimulus will be τ_1. Although τ_1 is negligible, $E\ \tau_1$ must be finite for a change in skin resistance to occur.

The initial condition ε_1 is the value of ε in equation (3) at $\tau = \tau_1$

$$\varepsilon_1 = AE(1 - e^{-\tau_1}).$$

Expanding $(1 - e^{-\tau_1})$ and taking only the linear terms in τ_1 leads to

$$\varepsilon_1 = AE\tau_1 \equiv q\,,$$

and this substituted in (5) gives

$$\varepsilon = qe^{-\tau} \tag{6}$$

which is the value of ε for $\tau > \tau_1$.

Since τ_1 is small, the chemical mediator, p_p, will remain unchanged for $0 < \tau < \tau_1$. But for $\tau > \tau_1$ it develops at a rate proportional to ε and is dissipated at a rate proportional to itself. Hence, we have

$$\frac{dp_p}{d\tau} = \xi\,\varepsilon - \mu\,p_p \tag{7}$$

where ξ and μ are constants of proportionality.

Substituting (6) in (7) and dropping all terms in τ_1 of higher order than the first, we have for the value of p_p

$$p_p = \frac{\xi q}{\mu - 1}\,(e^{-\tau} - e^{-\mu\tau}). \tag{8}$$

This is the value of the concentration of the chemical mediator of excitation at the peripheral end of the nerve.

The chemical diffuses to the region of the sweat glands where it modifies their permeability directly in proportion to its concentration. Designating its concentration (or the permeability of the sweat glands) as p_d, and letting p_o represent the inherent permeability of the tissue in the absence of a chemical mediator, we have

$$\frac{d(p_d - p_o)}{d\tau} = \alpha\,p_p - \mu(p_d - p_o) \tag{9}$$

where α and μ are constants of proportionality. Inasmuch as p_p and

$(p_d - p_o)$ represent the same substance or state, whatever it may be, at two different places, we have, as a first approximation, assumed their constants of proportionality (μ) in equation (7) and (9) to be equal.

Substituting (8) (9), integrating and defining

$$p_d = \bar{p} \text{ at } \tau = \tau_1$$

where $\bar{p}$ designates residual permeability remaining from previous stimulation, we obtain, after dropping all terms in τ_1 of higher order than the first,

$$p_d = p_o + (\bar{p} - p_o)\, e^{-\mu\tau} + \frac{\alpha\xi q}{(\mu - 1)^2}\left\{ e^{-\tau} - [1 - (1 - \mu)\tau]\, e^{-\mu\tau} \right\}. \quad (10)$$

If we assume that conductance (c) bears a direct linear relation to p_d

$$c = \frac{p_d}{k}$$

we obtain, by substituting in (10) and rearranging,

$$\frac{k}{p_o} c = 1 + \frac{(\bar{p} - p_o)}{p_o} e^{-\mu\tau} + \frac{\alpha\, \xi\, q}{(\mu - 1)^2 p_o}\left\{ e^{-\tau} - [1 - (1 - \mu)\tau]\, e^{-\mu\tau} \right\}. \quad (11)$$

The equation describing the variation of resistance (r) with time may be easily secured by substituting $c = 1/r$.

It is readily observed that at $\tau = 0$

$$c_o = \frac{\bar{p}}{k}, \quad (12)$$

and as $\tau \to \infty$

$$c_\infty \to \frac{p_o}{k}, \quad (13)$$

while the initial slope

$$\left.\frac{dc}{d\tau}\right|_{\tau=0} = -\frac{\mu}{k}(\bar{p} - p_o) = -\mu(c_o - c_\infty) \equiv S. \quad (14)$$

From a consideration of equations (12)-(14) certain interesting experiments suggest themselves.

1. Suppose a succession of instantaneous stimuli are presented the subject. For stimulus (i) the initial slope (S_i) and the initial conductance (c_{oi}) may be obtained. Substituting these values in equation (14) we have

$$-\mu(c_{oi} - c_\infty) = S_i ,$$

and similarly for stimulus (j)

$$-\mu(c_{oj} - c_\infty) = S_j .$$

Taking the ratios and solving for c_∞ we obtain

$$c_\infty = \frac{c_{oj}S_i - c_{oi}S_j}{S_i - S_j}. \tag{15}$$

As a consequence of the assumptions so far introduced, c_∞, obtained by equation (15) from the responses to any two stimuli (i, j), should be constant for a single subject. However, there is reason to believe (Richter, 1926b, 1929b), especially in the waking subject, that there is some degree of continuous excitation of the autonomic fibers mediating the galvanic skin response. Hence the excitation induced by stimulation of the subject in the laboratory will be superimposed on the more or less constant excitation existing at the moment.

Thus as $\tau \to \infty$

$$c_\infty \to \frac{p_o}{k} + \frac{p'}{k}$$

where p' represents the state of permeability of the tissue induced by the more or less constant level of excitation that prevails in the subject.

An alternative method of introducing the concept of p' is to introduce a positive constant E' in equation (2) and carry through the integrations in the same manner as before. Equation (15) when applied experimentally will yield a constant only if p' is constant. If p' varies in the course of an experiment, the values obtained in equation (15) will vary directly with it.

It may even be suggested that the lability of the parameter p' may be related to certain temperamental characteristics of the subject.

2. In order to obtain some qualitative estimate of the general nature of the time relations and the parameters of the function, we may differentiate equation (11) with respect to τ, and set it equal to zero. Doing this and rearranging terms, we obtain

$$e^{-(1-\mu)\tau} = -\mu(1-\mu)\tau + 1 - \frac{\mu(\bar{p} - p_o)(\mu - 1)^2}{\alpha \xi q}. \tag{16}$$

If we transform the time-units by

$$x = (1 - \mu)\tau ,$$

we have

$$e^{-x} = -\mu x + 1 - \frac{\mu(\bar{p} - p_o)(\mu - 1)^2}{\alpha \xi q}. \tag{17}$$

Then if we set

$$y = e^{-x}, \tag{18}$$

$$y = -\mu x + 1 - \frac{\mu(\bar{p} - p_o)(\mu - 1)^2}{\alpha \xi q}, \tag{19}$$

the intersection of the exponential curve and the straight line gives the value of x at which we have a maximum or minimum in the galvanic skin response. The following relations may be seen to hold in equations (18) and (19). For $\bar{p} > p_o$, other things being equal, as $(\bar{p} - p_o)$ increases, the latent time increases and the time to maximum conductance decreases. An approximate expression for the latent time under these conditions may be obtained by taking the first two terms of the expansion of the left hand side of equation (17), solving for x and substituting $(1 - \mu)\tau = x$. Doing this, we have

$$\tau' = \frac{\mu(\bar{p} - p_o)}{\alpha \xi q}$$

where τ' is the latent time.

For $\bar{p} < p_o$, the latent time cannot be secured from the equations, but as $\bar{p}$ decreases the time to maximum conductance increases.

Also, it may easily be seen from equations (18) and (19) that, other things remaining constant, for $\bar{p} > p_o$, as $q = AE\ \tau_1$ increases the latent time decreases, and the time to maximum conductance increases.

For $\bar{p} < p_o$, as $q = AE\tau_1$ increases the time to maximum conductance decreases. Nothing may be said with regard to the latent time for $\bar{p} < p_o$.

For $\bar{p} = p_o$, the time to maximum conductance is independent of the stimulus intensity.

3. For $\bar{p} > p_o$, if a subject be given successive equal stimuli (i), such that each stimulus occurs a few seconds after the point of maximum conductance is reached, but before recovery is complete, the initial slope (c_{oi}) of each successive response will be numerically greater, the magnitude of the response, measured in conductance, less than the preceding, the latent time will increase, and the time to maximum decrease.

From equation (14) it is obvious that as $(\bar{p} - p_o)$ increases, the initial slope increases numerically.

That the latency will increase and the time to maximum decrease has already been shown. This indicates that the duration of the excursion decreases, and it is reasonable that its magnitude also decreases. The limiting value for the duration of the excursion is zero as $(\bar{p} - p_o)$ increases, hence the limiting value of the magnitude of the excursion is zero.

For a given q, if $\bar{p}$ is very large, neither minimum nor maximum can occur. This means that the conductance can only decrease, despite the applied stimulus. Increasing the stimulus, however, will lead again to a maximum.

Inasmuch as q represents essentially the intensity of the stimulus applied to the autonomic fibers, it may or may not be a direct correlate of the physical intensity of the stimulus. With frequent successive presentations of the same physical stimulus, there may be some sort of central adaptation decreasing the effective value of q (Coombs, 1938).

The author wishes to acknowledge his appreciation of the aid of Dr. N. Rashevsky, who made this study possible, and of the many suggestions and criticisms of Dr. Alston S. Householder.

This work was aided in part by a grant from the Dr. Wallace C. and Clara A. Abbott Memorial Fund of the University of Chicago.

LITERATURE

Coombs, C. H. 1938. "Adaptation of the Galvanic Response to Auditory Stimuli." *J. Exper. Psych.*, **22**, 244-268.

Dale, H. H. 1936. "Some Recent Extensions of Chemical Transmission." *Symposia on Quant. Biol.*, **4**, 143-149.

Darrow, C. W. 1934. "Significance of Skin Resistance in the Light of Its Relation to the Amount of Perspiration." *J. Gen. Psych.*, **11**, 451-452.

O'Leary, W. D. 1932. "The Autonomic Nervous System as a Factor in the Psychogalvanic Reflex." *J. Exper. Psych.*, **15**, 767-772.

Rashevsky, N. 1938. *Mathematical Biophysics.* Chicago: The University of Chicago Press.

Richter, C. P. 1926. "The Significance of Changes in the Electrical Resistance of the Body During Sleep." *Proc. Nat. Acad. Sci.*, **12**, 214-222.

Richter, C. P. 1929a. "Nervous Control of the Electrical Resistance of the Skin." *Bull. Johns Hopkins Hosp.*, **45**, 56-74.

Richter, C. P. 1929b. "Pathologic Sleep and Similar Conditions." *Arch. Neurol. and Psychiat.*, **21**, 363-375.

BULLETIN OF
MATHEMATICAL BIOPHYSICS
VOLUME 3, 1941

A THEORY OF STEADY-STATE ACTIVITY IN NERVE-FIBER NETWORKS II: THE SIMPLE CIRCUIT

ALSTON S. HOUSEHOLDER
THE UNIVERSITY OF CHICAGO

It is found that for a simple circuit of neurons, if this contains an odd number of inhibitory fibers, or none at all, or if the product of the activity parameters is less than unity, then the stimulus pattern always determines uniquely the steady-state activity. For circuits not of one of these types, it is possible to classify exclusively and exhaustively all possible activity patterns into three types, here called "odd", "even", and "mixed". For any pattern of odd type and any pattern of even type there always exists a stimulus pattern consistent with both, but in no other way can such an association of activity patterns be made.

In continuation of an investigation previously introduced (Householder, 1941; this paper will be designated "I", hereafter), we consider here n simple neurons (each having a single axon and a single dendrite) which we shall designate $(1), (2), \cdots, (n)$, arranged in a simple circuit so that fiber (i) synapses with fiber $(i + 1)$. We shall, when convenient, use the notation (i) and $(n + i)$ interchangeably to denote the same fiber. We suppose that if a constant stimulus S_i is applied to neuron (i), and if S_i exceeds the threshold h_i of this neuron, then, in the absence of other factors, this neuron tends asymptotically to a steady-state activity in which it develops $\varepsilon - j$ in the amount $a_i(S_i - h_i)$. (For terms and symbols not here defined see Rashevsky, 1940, and I.)

It should be pointed out that whereas we speak here of single neurons reaching a steady-state of activity, this is not the only possible physical realization of the equations and relations assumed. Thus it may be that a small bundle of several parallel fibers is involved, instead of a single one, so associated that while adaptation leads to a periodic inactivity of one or another fiber of this bundle, the activity is taken over by other fibers of the bundle, the net effect being one of steady activity. Again, an inhibitory fiber may be a fiber or bundle of fibers so related to the next fiber or bundle that its activity serves always to depress these. In this connection cf. N. Rashevsky (1940, chap. viii).

The constant a_i, which may be positive or negative, but is not null (when any $a_i = 0$, there is no problem), is called the *activity para-*

meter of the neuron. Hence, if at each synapse a constant stimulus S_i is applied from a source which is independent of the activity of neurons of the circuit the total stimulus η_i acting upon (i) is the sum of S_i and the contribution of the fiber $(i-1)$. By setting

$$y_i = \eta_i - h_i\,, \qquad \sigma_i = S_i - h_i\,,$$

as in I, the activity of the circuit is described by the equations

$$y_i = \sigma_i + a_{i-1}\, y_{i-1}\,, \tag{1}$$

where

$$\begin{aligned} a_j &= 0 \quad \text{when} \quad y_j \leqq 0\,, \\ a_j &= a_j \quad \text{when} \quad y_j > 0\,. \end{aligned} \tag{2}$$

The vectors

$$\alpha = (a_1, \cdots, a_n), \quad y = (y_1, \cdots, y_n), \quad \sigma = (\sigma_1, \cdots, \sigma_n) \tag{3}$$

we shall call, respectively, the *activity pattern* (*AP*), the *excitation pattern* (*EP*), and the *stimulus pattern* (*SP*) of the circuit. This terminology deviates slightly from that employed in I. Evidently y determines uniquely α and σ; also σ and α together determine uniquely y. But not every pair of vectors σ and α determine a y by (1) which is consistent with (2). When they do, we shall say that σ and α are *consistent.* In fact, one result in I was to the effect that for circuits containing only excitatory neurons (all $a_i > 0$), there is one and only one α consistent with any given σ.

It is evident from (2) that α is known when its null components are known, since its other components are equal to the corresponding a_i. If $a_k = 0$, we shall say that α, or the *AP, has a zero at k,* or that *k is a zero of* α. Another result of I was to the effect that if two vectors α and β are *AP*'s having a common zero, and if both are consistent with some σ, then $\alpha = \beta$. *We shall consider here only* AP's α *with at least one zero,* and the problem is, for a given circuit, if α has at least one zero, how many *AP*'s β are there, each of which has at least one zero, and each of which is consistent with some σ with which α is itself consistent? Or, given σ, with how many *AP*'s, each containing at least one zero, is it consistent?

Thus along with (1) and (2), we consider

$$z_i = \sigma_i + \beta_{i-1}\, z_{i-1} \tag{4}$$

where

$$\begin{aligned} \beta_j &= 0 \quad \text{when} \quad z_j \leqq 0\,, \\ \beta_j &= a_j \quad \text{when} \quad z_j > 0\,. \end{aligned} \tag{5}$$

We suppose $\alpha \neq \beta$. Hence no k is a zero of both α and β. As in I, we define

$$\begin{aligned} \sigma_i^{(1)} &\equiv \sigma_i\,, \\ \sigma_i^{(\nu)} &\equiv \sigma_i^{(1)} + a_{i-1}\,\sigma_{i-1}^{(\nu-1)}\,. \end{aligned} \tag{6}$$

Hence

$$\sigma_i^{(\nu)} = \sigma_i^{(\rho)} + a_{i-1}\,a_{i-2}\cdots a_{i-\rho}\,\sigma_{i-\rho}^{(\nu-\rho)}\,. \tag{7}$$

From the matrix $(\sigma_i^{(\nu)})$ pick out the set

$$\sigma_1^{(\lambda_1)}, \sigma_2^{(\lambda_2)}, \cdots, \sigma_n^{(\lambda_n)} \tag{8}$$

by means of the conditions

$$\begin{aligned} \lambda_{i+1} &= 1 + \lambda_i \quad \text{when} \quad \alpha_i \neq 0\,, \\ \lambda_{i+1} &= 1 \qquad\quad \text{when} \quad \alpha_i = 0\,. \end{aligned} \tag{9}$$

Then, as we have seen in I, if α is, in fact, consistent with σ, it must be true that

$$y_i = \sigma_i^{(\lambda_i)} \tag{10}$$

satisfy (1) consistently with (2), and hence

$$\begin{aligned} \sigma_i^{(\lambda_i)} &\leqq 0 \quad \text{when} \quad \alpha_i = 0\,, \\ \sigma_i^{(\lambda_i)} &> 0 \quad \text{when} \quad \alpha_i = a_i\,. \end{aligned} \tag{11}$$

In like manner we determine the set

$$\sigma_1^{(\mu_1)}, \sigma_2^{(\mu_2)}, \cdots, \sigma_n^{(\mu_n)} \tag{12}$$

by means of the conditions

$$\begin{aligned} \mu_{i+1} &= 1 + \mu_i \quad \text{when} \quad \beta_i \neq 0\,, \\ \mu_{i+1} &= 1 \qquad\quad \text{when} \quad \beta_i = 0\,; \end{aligned} \tag{13}$$

equations (1) have the solutions

$$z_i = \sigma_i^{(\mu_i)} \tag{14}$$

consistent with (5), and

$$\begin{aligned} \sigma_i^{(\mu_i)} &\leqq 0 \quad \text{when} \quad \beta_i = 0\,, \\ \sigma_i^{(\mu_i)} &> 0 \quad \text{when} \quad \beta_i \neq 0\,. \end{aligned} \tag{15}$$

The operations just carried out may be conveniently represented as follows. Consider a cylindrical surface of circumference n and altitude n, and the lattice of points with positive integral coordinates. The lattice point whose abscissa is i and whose ordinate is λ may be associated with the element $\sigma_i^{(\lambda)}$ of the matrix of σ's. With any AP,

α, we may associate a curve on this cylinder, the curve consisting entirely of helical arcs joining the points (i, λ_i) as the λ_i are defined by (9). Thus all ascending arcs of the curve become lines of unit slope when the cylindrical surface is slit along a generator and flattened out onto a plane. And every arc is an ascending arc except those leading from points of abscissa i for which $\alpha_i = 0$. Hence if $\alpha_i = 0$ we may speak of the point (i, λ_i) as being a (relative) peak, and it is an actual peak unless also $\alpha_{i-1} = 0$. Thus every relative peak of this curve marks a zero of the *AP*, α, and conversely.

Associated with any other *AP*, β, will be a similar curve, and these two curves may be called the α-curve and the β-curve respectively. Then if α and β are both consistent with some σ, no peak of the α-curve can have the same abscissa as a peak of the β-curve. Hence while the two curves must cross, they can have no common arc and no common lattice point. This representation is not essential to the ensuing discussion, but it may serve to clarify some of the statements.

We prove first

LEMMA 1. *If the* AP's α *and* β, *each containing at least one zero, are both consistent with the* SP σ, *and if* α (*or* β) *has zeroes at* h *and* k, *then*

$$a_h a_{h+1} \cdots a_{k-1} > 0, \qquad a_k a_{k+1} \cdots a_{h-1} > 0, \tag{16}$$

while if h *and* k *are zeroes, one of* α, *the other of* β, *then*

$$a_h a_{h+1} \cdots a_{k-1} < 0, \qquad a_k a_{k+1} \cdots a_{h-1} < 0, \tag{17}$$

any subscript exceeding n *being reduced by* n. *As a special case of* (16) *it follows that*

$$a_1 a_2 \cdots a_n > 0. \tag{18}$$

First, suppose i and $i + \nu$ are zeroes of α, but that the sequence $i + 1, i + 2, \cdots, i + \nu - 1$ contains no zero of either α or β. Then it follows from (9) and (13) that

$$\lambda_{i+\rho} = \rho, \quad \mu_{i+\rho} = \mu_i + \rho \qquad (\rho = 1, \cdots, \nu); \tag{19}$$

from (11) it follows that

$$\sigma_{i+\nu}^{(\nu)} \leqq 0, \quad \sigma_{i+\rho}^{(\rho)} > 0 \qquad (\rho = 1, \cdots, \nu - 1), \tag{20}$$

and from (15) that

$$\sigma_{i+\rho}^{(\mu_{i+\rho})} > 0 \qquad (\rho = 1, \cdots, \nu). \tag{21}$$

Finally we have from (7) that

$$\sigma_{i+\rho}^{(\mu_{i+\rho})} = \sigma_{i+\rho}^{(\rho)} + a_{i+\rho-1} a_{i+\rho-2} \cdots a_i \, \sigma_i^{(\mu_i)} \qquad (\rho = 1, \cdots, \nu). \tag{22}$$

With $h = i$, $k = i + \nu$, the first of (16) follows in this special case from (20), (21) and (22) when $\rho = \nu$.

Next suppose that $i + \nu + \nu'$ is the next zero of α, and that the set $i + \nu + 1, i + \nu + 2, \cdots, i + \nu + \nu' - 1$ contains no zero of either α or β. Then

$$a_i a_{i+1} \cdots a_{i+\nu-1} > 0, a_{i+\nu} a_{i+\nu+1} \cdots a_{i+\nu+\nu'-1} > 0,$$

and therefore the first of (16) follows with $h = i$, $k = i + \nu + \nu'$. By a simple induction the first of (16) can be proved in all cases where the set $h + 1, h + 2, \cdots, k-1$ contains no zero of β.

Before proceeding with (16) we consider (17). Let i be a zero of α, $i + \nu$ of β, and suppose that the sequence $i + 1, i + 2, \cdots, i + \nu - 1$ contains no zero of either α or β. Then (19) and (22) still hold, but in place of (20) and (21) we have

$$\sigma_{i+\rho}^{(\rho)} > 0 \qquad (\rho = 1, \cdots, \nu), \tag{23}$$

$$\sigma_{i+\nu}^{(\mu_i+\nu)} \leqq 0, \qquad \sigma_{i+\rho}^{(\mu_i+\rho)} > 0 \qquad (\rho = 1, \cdots, \nu - 1). \tag{24}$$

Then with $h = i$, $k = i + \nu$, the first of (17) follows in this special case by taking $\rho = \nu$ in (22), (23) and (24). But now the induction can be completed, for if we pick out from the sequence $h, h + 1, \cdots, k - 1, k$, all those terms $h_1 = h, h_2, \cdots, h_p = h$, each of which is a zero of either α or β, then in the hypothesis for (16) there will be an even number of pairs of consecutive terms of this subsequence, h_r and h_{r+1}, of which one is a zero of α and the other of β; while under the hypothesis for (17) there will be an odd number of such.

COROLLARY 1. *If the circuit contains an odd number of inhibitory fibers (the number of negative* a_i *is odd) or if it has none, then for any* SP σ *there cannot be more than one* AP α *which contains at least one zero and is consistent with* σ. *Moreover* y *and* α *can be determined from the matrix of the* $\sigma_1^{(\lambda)}$.

We, therefore, consider only circuits which contain an even number of inhibitory fibers in the sequel. Let there be $2m$ inhibitory fibers and $\mu = n - 2m$ excitatory fibers. Suppose the inhibitory fibers are

$$(i_1), (i_2), \cdots, (i_{2m})$$

and the excitatory fibers

$$(j_1), (j_2), \cdots, (j_\mu),$$

and suppose that

$$1 \leqq i_1 < i_2 < \cdots < i_{2m} \leqq n,$$

$$1 \leqq j_1 < j_2 < \cdots < j_\mu \leqq n.$$

Let α be any *AP* with at least one zero and let k be one of its zeroes. Then there is a smallest integer κ (which may be zero) for which $k + \kappa$ (or $k + \kappa - n$) is equal to some $i_r (r = 1, \cdots, 2m)$. We shall say that the zero at k, or that the fiber (k) is *of even type* when r is an even number, and that it is *of odd type* when r is an odd number. Evidently a change in the enumeration of the neurons will either interchange all types or else leave them all fixed. If α has zeroes of even type only then α will be said to be of *even type*; if α has zeroes of odd type only then α will be said to be of *odd type*; if α has zeroes of both types, α will be said to be of mixed type. Then it is only a restatement of lemma 1 to say

LEMMA 2. *If the* AP's α *and* β, *each containing at least one zero, are both consistent with some* SP σ, *then either* α *is of odd type and* β *of even type, or vice versa. In particular, no* SP σ *can be consistent with more than two* AP's *and if it is consistent with any* AP *of mixed type, then it is consistent with this alone.*

We have yet to see whether, given an *AP* α of odd type and an *AP* β of even type, it is always possible to find a σ consistent with both. Before doing this we must examine further the conditions which we imposed upon the σ's when this is to hold. These relations can be summarized thus:

LEMMA 3. *If* α *and* β *are two* AP's, *each containing at least one zero and each consistent with the* SP σ, *and*

a) *if* h *and* k *are zeroes of* α, *then*

$$z_k \leqq a_{k-1}\, a_{k-2} \cdots a_h\, z_h; \tag{25}$$

b) *if* h *and* k *are zeroes of* β, *then*

$$y_k \leqq a_{k-1} \cdots a_h\, y_h; \tag{26}$$

c) *if* h *is a zero of* α *and* k *is a zero of* β, *then*

$$y_k \leqq -a_{k-1} \cdots a_h\, z_h; \tag{27}$$

d) *if* h *is a zero of* β *and* k *a zero of* α, *then*

$$z_k \leqq -a_{k-1} \cdots a_h\, y_h. \tag{28}$$

The y_i *and* z_i *are understood to be the solutions of* (1) *and* (4).

Bearing in mind equations (10) and (14), we proceed as in the proof of lemma 1. If i and $i + \nu$ are zeroes of α, but the sequence, $i + 1, \cdots, i + \nu - 1$ contains no zero of α or of β, then (19)—(22) hold, and these, for $\rho = \nu$, give (25) in this special case. If i is a zero of α, $i + \nu$ of β, and the sequence $i + 1, \cdots, i + \nu - 1$ contains no zero

of either α or of β, then (19) and (22)—(24) hold and we have (27) in this special case. By interchanging the roles of α and β we obtain (26) and (28) in the corresponding special cases. In the general case we pass from zero to zero applying the special formulas, and so obtain the desired result by induction.

If we take $h = k$ in either (25) or (26), then since $z_h > 0$ or $y_h > 0$ as the case may be, we have

COROLLARY 2. *If there exist two* AP's, α *and* β, *each having at least one zero, and an* SP σ *consistent with both, then*

$$a_1 a_2 \cdots a_n \geqq 1 . \tag{29}$$

These results can now be summarized and completed.

THEOREM. *Let a circuit be given which has in it at least two inhibitory neurons, and let the activity parameters of the neurons satisfy* (29). *Let* α *be any* AP *of odd type and* β *any* AP *of even type. Then there always exists an* AP σ *consistent with both of them. But for no other type of circuit, and for no other kind of pairing of* AP's *can such a* σ *be found.*

Having given the zeroes of each *AP*, we can determine the superscripts λ_i and μ_i of (10) and (14). At all the zeroes h of α and β there are relations of the form (25)—(28) restricting the values of the y_h and z_h. These are consistent provided only (29) holds, although if the equality sign holds in (29) it must also be taken in (25)—(28) and then the choice of a single y_h or z_h prescribes the values of all the others.

Between pairs of zeroes, i and $i + \nu$, we have relations of the form

$$z_{i+\rho} = y_{i+\rho} + a_{i+\rho-1} \cdots a_i \, z_i \tag{30}$$

if i is a zero of α, and of the form

$$y_{i+\rho} = z_{i+\rho} + a_{i+\rho-1} \cdots a_i \, y_i \tag{31}$$

if i is a zero of β, as follows from (22). By setting $\rho = \nu$, it follows that having chosen the y_h and z_k occurring in (25)—(28), the y_k and z_h at the zeroes are also fixed. Now inequalities (20), (21), (23), (24) and their analogues with α and β interchanged, and with $\rho \neq \nu$ when expressed in terms of the y's and z's, impose lower limits on these, but not upper limits. Hence these are always consistent and for each ρ, either $y_{i+\rho}$ or $z_{i+\rho}$ can be chosen, and the other one is fixed. The σ_i are uniquely determined once the y_i (or z_i) have been fixed.

We conclude by noting that if, among the μ excitatory fibers (j_1), $\cdots$, (j_n), there are μ_1 of odd type and $\mu_2 = \mu - \mu$, of even type, then there are

$$2^{m+\mu_1} - 1$$

distinct *AP*'s α of odd type and

$$2^{m+\mu_2} - 1$$

distinct *AP*'s β of even type. Hence if (29) holds there are

$$(2^{m+\mu_1} - 1)\,(2^{m+\mu_2} - 1)$$

ways in which a pair of *AP*'s α and β can be found both of which are consistent with some *SP* σ.

As a simple illustration of the foregoing, consider a circuit of four fibers. If the number of inhibitory fibers in this circuit is 0, 1, or 3, or if $a_1a_2a_3a_4 < 1$, then any σ is consistent with at most one *AP* having at least one zero. Suppose, however, that

$$a_1 > 0\,, \quad a_2 > 0\,, \quad a_3 < 0\,, \quad a_4 < 0\,, \quad a_1a_2a_3a_4 > 1\,.$$

Then (4) alone is of even type, (1), (2) and (3) are of odd type. Hence $\mu_1 = 2$, $\mu_2 = 0$, $\nu = 1$, and there are $2^3 - 1 = 7$ *AP*'s of odd type, $2^1 - 1 = 1$ *AP*'s of even type. The latter is of the form $(a_1, a_2, a_3, 0)$; the others are of the form $(\alpha_1, \alpha_2, \alpha_3, a_4)$, where at least one α is zero, and any one of these is consistent with some σ which is consistent with the single *AP* of even type, but not with any σ which is consistent with any other *AP*. Moreover no *AP* of the type $(\alpha_1, \alpha_2, \alpha_3, 0)$, where at least one of the α's is zero, is consistent with any σ which is consistent with any other *AP*.

In the circuit for which $a_1 > 0$, $a_2 < 0$, $a_3 > 0$, $a_4 < 0$, there are three *AP*'s of odd type of the form $(\alpha_1, \alpha_2, \alpha_3, a_4)$, and three of even type of the form $(a_1, \alpha_2, \alpha_3, \alpha_4)$, and if any *AP* of odd type is associated with any *AP* of even type, a σ can be found which is consistent with both, provided $a_1\, a_2\, a_3\, a_4 \geqq 1$.

This work was aided in part by a grant from the Dr. Wallace C. and Clara A. Abbott Memorial Fund of the University of Chicago.

LITERATURE

Householder, Alston S. 1941. "A Theory of Steady-State Activity in Nerve-Fiber Networks: I. Definitions and Preliminary Lemmas." *Bull. Math. Biophysics*, 3, 63-69.

Rashevsky, N. 1940. *Advances and Applications of Mathematical Biology*. Chicago: The University of Chicago Press.

SCOPE OF THE BULLETIN

1. The Bulletin is devoted to publications of research in Mathematical Biophysics, as contributing to the physicomathematical foundations of biology in their most general scope.

2. Papers published in the Bulletin cover physicomathematical theories as well as any other mathematical treatments of biological phenomena, with the exception of purely statistical studies.

3. Mathematical studies in physics or in borderline fields in which a direct connection with biological problems is pointed out are also accepted.

4. Emphasis is put upon the mathematical developments, but a description and discussion of experimental work falls also within the scope of the Bulletin provided that description or discussion is made in close connection with mathematical developments *contained in the same paper.*

5. Outside of the scope of the journal are papers of purely statistical nature or papers concerned only with empirical equations.

PREPARATION OF MANUSCRIPTS

All manuscripts should be typewritten double space. Equations should be numbered on the right consecutively. *Do not* use such notations as "equation 2a" or, "equation 5′ " etc. References should be all given at the end of the paper, arranged in alphabetic order by authors and for each author chronologically, following *exactly* the style used in the Bulletin. In text, reference should be made by giving in parentheses the name of the author followed by the year of publication. In case of several publications by the same author in the same year, use notations "1940a", "1940b", etc.

In writing equations, slanted lines should be used wherever possible.

Every paper is to be preceded by a short abstract.

Drawings should be prepared in a professional manner on white paper or tracing cloth following as closely as possible the style used in the Bulletin. They should be drawn approximately twice the scale of the finished reproduction. Lettering should be made by means of a lettering guide. If desired by the authors, drawings may be made at the Editorial Office according to author's instructions, at cost.